Tandem E2F binding sites in the promoter of the p107 cell cycle regulator control p107 expression and its cellular functions.

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Public Summary:

Scientific Abstract:
The retinoblastoma tumor suppressor (Rb) is a potent and ubiquitously expressed cell cycle regulator, but patients with a germline Rb mutation develop a very specific tumor spectrum. This surprising observation raises the possibility that mechanisms that compensate for loss of Rb function are present or activated in many cell types. In particular, p107, a protein related to Rb, has been shown to functionally overlap for loss of Rb in several cellular contexts. To investigate the mechanisms underlying this functional redundancy between Rb and p107 in vivo, we used gene targeting in embryonic stem cells to engineer point mutations in two consensus E2F binding sites in the endogenous p107 promoter. Analysis of normal and mutant cells by gene expression and chromatin immunoprecipitation assays showed that members of the Rb and E2F families directly bound these two sites. Furthermore, we found that these two E2F sites controlled both the repression of p107 in quiescent cells and also its activation in cycling cells, as well as in Rb mutant cells. Cell cycle assays further indicated that activation of p107 transcription during S phase through the two E2F binding sites was critical for controlled cell cycle progression, uncovering a specific role for p107 to slow proliferation in mammalian cells. Direct transcriptional repression of p107 by Rb and E2F family members provides a molecular mechanism for a critical negative feedback loop during cell cycle progression and tumorigenesis. These experiments also suggest novel therapeutic strategies to increase the p107 levels in tumor cells.